Towards de-escalation of axillary management after neoadjuvant chemotherapy in breast cancer

VALORISATION

Breast cancer is the most commonly diagnosed cancer amongst women worldwide. In the Netherlands, approximately 16.000 patients are diagnosed with invasive breast cancer each year. Survival rates of these patients have increased substantially over the past decades and are still improving with the development of new therapies (such as immunotherapy). With increasing numbers of breast cancer survivors, improving quality of life becomes more and more important. About 20% of newly diagnosed patients are treated with neoadjuvant chemotherapy and these rates increased gradually over the past years. Currently, there is much debate on what constitutes the optimal axillary management in patients treated with neoadjuvant chemotherapy. On the one hand, specialists are striving for a least invasive strategy, on the other hand, specialists can't justify improving quality of life at the expense of oncologic safety. The aim of this thesis was to help shape response-based axillary management.

Relevance of scientific results in this thesis

This thesis evaluated current practices and trends regarding axillary management in patients with breast cancer treated with neoadjuvant chemotherapy. Especially in node positive breast cancer, the management of the axilla is an area of controversy. Traditionally, an axillary lymph node dissection was always performed. However, when clinically node positive patients are treated with neoadjuvant chemotherapy, a substantial part achieves a pathologic complete response of the axilla. These patients will probably not benefit from an axillary lymph node dissection. This thesis therefore focused on identifying the most optimal less invasive surgical procedure for axillary staging after neoadjuvant chemotherapy in node positive breast cancer patients. The systematic review and meta-analysis we performed, showed that a combination of sentinel lymph node biopsy with the MARI-procedure is the most optimal procedure in terms of identification rate and accuracy (false negative rate and negative predictive value). Importantly, only 2 studies addressed the accuracy of a combination procedure and only 1 study that of the MARI procedure, compared to 17 studies for the sentinel lymph node biopsy. Despite convincing evidence, axillary lymph node dissection is already being replaced by different less invasive procedures in daily practice at some institutions. This also occurs in the Netherlands, as we confirmed in chapter 2 of this thesis. To take optimal use of this ongoing trend, we evaluated a cohort of patients in whom axillary lymph node dissection is already being replaced by a combination procedure in daily practice. In this study, we found that the sentinel lymph node biopsy and MARI procedure complement each other, resulting in an improved identification rate and improved detection of residual axillary disease. Both the results of the systematic review and this cohort study, provide valuable considerations for specialists who already have implemented or who are about to

start implementing a less invasive staging procedure in daily practice. Based on the findings of these two studies, performing a combination procedure is recommended instead of performing either sentinel lymph node biopsy or the MARI procedure alone when omission of axillary lymph node dissection is considered.

Target population

The results of this thesis provide breast cancer specialists with insights in current practices worldwide regarding axillary management in patients treated with neoadjuvant chemotherapy. It furthermore provides steppingstones for specialists to help shape their local protocols regarding management of the axilla. Apart from this, the results of this thesis are helpful for patients diagnosed with breast cancer. The results can be used to inform patients accordingly and may aid in shared-decision making. While patients should be informed on the side effects of axillary lymph node dissection, they certainly should also be informed on the lack of evidence regarding oncologic safety of less invasive staging procedures. With the results of this thesis, we furthermore demonstrated that patients may receive a different axillary management plan dependent on where or by whom they are treated. Patients should be aware of this and informed accordingly by the treating specialist. These results stress the importance of continuing to join efforts to encourage patients to participate in clinical trials or registry studies. Ultimately, evidence-based guidelines can be determined to provided patients with a personalized - yet consistent amongst institutions – axillary staging and management plan that is optimal in terms of quality of life and oncologic safety.

Innovation and future

Although combining sentinel lymph node biopsy with a MARI-like procedure has been reported before, the RISAS trial is the first trial to validate such a combination procedure following a prospective and multicenter study design. Furthermore, a large cohort of 225 patients will be included. The results of this trial will confirm whether a combination procedure is indeed the most accurate less invasive axillary staging procedure for node positive breast cancer patients treated with neoadjuvant chemotherapy. If this procedure is proven to be accurate, these results will be implemented in guidelines worldwide. Consequently, more patients can benefit from a less invasive procedure and be spared the high risk of comorbidity that is associated with axillary lymph node dissection. Future research has to determine what kind of combination procedure is most optimal in terms of accuracy, cost-effectiveness and patient-friendliness. The MINIMAX trial, which will start accruing in the near future, will take the next step in providing evidence on the appropriate staging and treatment procedures concerning prognosis and quality of life. A less invasive staging procedure

is already standard of care for cN+ patients treated with NST in many institutions. In other institutions the axillary lymph node dissection is still routinely performed. Consequently, a nationwide cohort of cN+ patients can be developed to compare less and more invasive axillary staging and treatment procedures. Therefore, a multicenter, retro- and prospective, observational, registry study will be initiated in cN+ breast cancer patients treated with NST in the Netherlands. The primary aim is to determine five- and ten-year disease-free survival, breast cancer-specific survival, overall survival, and axillary recurrence rates, for the less and more invasive axillary staging and treatment procedures. The secondary aim is to determine their effect on QoL, assessed at baseline, at one year and at five years after diagnosis. The first results of the MINIMAX trial are expected in 2023.